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9419715.9 **30 September 1994 (30.09.94)** **GB**(71) Applicant (for all designated States except US): **THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).**

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(57) Abstract

The invention provides the use of one or more of the following substances as hair stimulants: 1) a water-soluble potassium, copper and/or zinc salt, suitably being an acetate salt; 2) a flavone or flavone derivative, suitably comprising rutin, such as roxerutin; 3) a xanthine, such as a theophylline, or a derivative thereof, such as methyl silanol theophyllin acetate alginate; 4) a mucopolysaccharide or derivative thereof such as dimethylsilanol hyaluronate; 5) a fat soluble vitamin or a derivative thereof such as vitamin A (retinol) palmitate or vitamin E (tocopherol); 6) Zedoary, ginger, and/or cinnamon oil; or combinations of these; 7) an allyl-based plant extract such as onion or garlic extract, such as onion extract in coconut oil or garlic extracted in butylene glycol.

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HAIR STIMULANT COMPOSITION

The present invention relates to a composition for use as a hair stimulant, to a method of modifying hair growth and/or hair loss, and to uses of substances and/or compositions as hair stimulants.

The term "hair stimulant" as used herein means a substance or composition which either stimulates hair growth and/or inhibits hair loss in humans, especially on the scalp.

10 Loss of scalp hair is a normal phenomenon which occurs when the hair follicle comes to the end of its growth phase and enters a resting phase before re-starting the growth cycle. On the human scalp, follicles are not growing synchronously and around 10% will be in the resting (telogen) phase at any one time. Thus normal loss will cause no noticeable alteration in scalp hair coverage. The normal ageing process sees an increase in the number of telogen follicles and results in the thinning of hair. The process is more pronounced in males, leading to the largely accepted theory that the male hormone testosterone and its more active metabolite 5 α -dihydrotestosterone have a role in what is known as male pattern baldness.

25 Ageing is not the only cause of hair loss. It can also have pathological causes, as in the condition known as alopecia areata, with a variety of clinical presentations and prognoses in which autoimmunity is thought to play a part. Hair loss may also occur in a number of other circumstances, such as when a patient is treated with cytotoxic drugs or undergoes radiotherapy.

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Some drugs are known to stimulate hair growth. An example is the drug minoxidil which, although originally developed as an antihypertensive, subsequently became a product (marketed under the Trade Name "Regaine") used with some success in promoting new hair growth.

There remains a need, however, for further means of stimulating hair growth and/or inhibiting hair loss.

According to the present invention, there is provided the use of one or more of the following substances ("the substances listed") as hair stimulants:

- 1) A water-soluble potassium, copper and/or zinc salt, suitably being an acetate salt;
- 2) A flavone or flavone derivative, suitably comprising rutin, such as troxerutin;
- 15 3) A xanthine, such as a theophylline, or a derivative thereof, such as methyl silanol theophyllin acetate alginate;
- 4) A mucopolysaccharide or derivative thereof such as dimethylsilanol hyaluronate;
- 20 5) A fat soluble vitamin or a derivative thereof such as vitamin A (retinol) palmitate or vitamin E (tocopherol);
- 6) Zedoary, ginger, and/or cinnamon oil; or combinations of these;
- 25 7) An allyl-based plant extract such as onion or garlic extract, such as onion extract in coconut oil or garlic extracted in butylene glycol.

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Suitably, at least two, preferably at least three or more of the substances listed are used together, either simultaneously or sequentially.

5 There is also provided the use of any one, preferably two or three, of the substances listed in the manufacture of a medicament for the treatment of hair loss, such as alopecia areata.

10 There is further provided a method of treating hair loss (such as alopecia areata) by applying a flavone, a xanthine such as theophylline or a derivative thereof and at least one, suitably at least two of the other substances listed to the scalp. The substances may be applied either simultaneously or sequentially, but simultaneous application is preferred. The method may
15 be used for medical and/or cosmetic purposes.

The invention further provides a composition for stimulating hair growth and/or inhibiting hair loss in humans, comprising a flavone, a xanthine such as theophylline or a derivative thereof and at least one,
20 suitably at least two of the other substances listed, for simultaneous or sequential administration to the scalp.

The substances listed are suitably included in compositions to the following concentrations (all w/w%)

- 25 1) 0.01 to 0.5%, suitably about 0.05%;
2) 0.01 to 0.5%, suitably about 0.1%;
3) 0.1 to 5%, suitably about 1%;
4) 0.1 to 5%, suitably about 1%;
5) 0.01 to 1%, suitably about 0.05%;
30 6) 0.1 to 5%, suitably about 0.5%; and
7) 0.01 to 1%, suitably about 0.1%

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respectively wherein the numbering corresponds to the numbering used above.

The composition may comprise said components either in the form of a mixture, or in a physically separate
5 state either for admixture prior to simultaneous application or for separate/sequential application to the scalp.

Suitably, the composition may be in the form of a shampoo, conditioner, hair gel, styling gel, hair cream
10 or lotion, hair mousse, hairspray or hair lacquer.

It will be understood that further components may be added to the composition as is well-known in the art.

For example, preservatives may be present, such as bronopol, benzyl alcohol, imidazolidinyl urea, methyl
15 paraben, propyl paraben, and naturally occurring preservatives such as the enzyme lactoperoxidase, particularly the blend of lactoperoxidase, glucose, glucose oxidase, iodide and thiocyanate marketed by The Boots Company PLC under the Trade Name "Myavert-C".
20 Suitably such preservatives are included in an amount of from about 0.01% to about 2% by weight of the composition.

Styling gels may comprise resins such as polyvinyl pyrrolidone in a Carbopol gel and D-panthenol and/or
25 propylene glycol as a conditioning aid.

Thickeners and viscosity modifying agents may be present, such as 1,3-butylene glycol, quaternised methyl-hydroxycellulose, amine oxides, block polymers of ethylene oxide and propylene oxide (for example, those
30 available from BASF Wyandotte under the Trade Name

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"Pluronic"), polyvinyl alcohols and fatty alcohols, suitably in an amount of from about 0.5% to about 10% by weight of the composition.

5 Surfactants may be present, such as silicone glycol copolymer, anionics such as sodium laurylether sulphates, amphoterics such as cocoa amidopropyl betaines, sarcosinates and sulphosuccinates.

10 Conditioning agents include proteins, protein hydrolysates, for example the blend of soya amino acids available from Croda Chemicals under the Trade Name "Hydrosoy 2000"; clays, for example the montmorillonite clay available from English China Clays under the Trade Name "Col White HNF"; and quaternary ammonium compounds such as Dehyquart A.

15 Sequestering agents may be present, such as ethylenediamine tetraacetic acid and salts thereof, suitably in an amount of from about 0.005 % to about 0.5% by weight of the composition.

20 Perfumes may be present, suitably in an amount of from about 0.01% to about 2%, as may water soluble dyes such as tartrazine, suitably in an amount of from about 0.00001% to about 0.1% by weight of the composition.

• The composition may be buffered by means well known in the art, for example by use of buffer systems
25 comprising succinic acid, citric acid, lactic acid, phosphoric acid, mono- or disodium phosphoric and sodium carbonate. Suitably, the composition may have a pH between about 3 and about 10, preferably between about 4 and about 6.

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The composition may also include an antidandruff agent such as salicyclic acid or zinc pyrithione suitably in an amount of from about 0.1% to about 5% by weight.

- 5 Cosmetic components, such as D-panthenol, henna extracts, soya amino acids and fruit extracts may be included as is well known in the art.

The invention will be understood with reference to the following non-limiting example:

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Example 1 Hair stimulant composition

A hair stimulant composition was prepared as follows:

5	<u>Component</u>	<u>Concentration</u>
		<u>(w/w%)</u>
	Potassium acetate	0.10
	Copper (II) acetate	0.05
	Zinc acetate	0.05
	Troxerutin	0.10
10	Methyl silanol theophyllin acetate alginate (available from Exsymol Ltd under the Trade Name "Theophyllisilane C")	1.00
	Dimethyl silanol hyaluronate (available from Exsymol Ltd under the Trade Name "DSH C")	1.00
15	D-Panthenol	0.50
	Silicone Glycol Copolymer (available from Dow Corning under the Trade Name "Dow Corning 193")	1.50
20	Mixture of Zedoary, ginger and cinnamon oil (available from VEVY under the Trade Name "Zedomina")	0.50
	Vitamin A palmitate	0.05
	Vitamin E (available from Henkel under the Trade Name "Copherol F1300")	0.05
25	Cyclomethicone 100 centistoke silicone fluid	1.00
	1,3-butylene glycol	5.00
	Quaternised methyl hydroxycellulose (available from Courtaulds under the Trade Name "DP969")	0.50
30	Soya amino acids (available from Croda Chemicals under the Trade Name "Hydrosoy 2000")	0.25
	Onion extract and coconut oil (available from VEVY under the Trade Name	0.10
35	"Allum Cepa")	

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METHOD OF PREPARATION

1. Oil soluble components - Zedoary extracts, onion extract, vitamin A palmitate, vitamin E and silicone glycol copolymer, were mixed with gentle heat.
2. Aqueous components were separately mixed with simple stirring in the following order - inorganic salts, flavonoid, theophylline derivative, mucopolysaccharide.
3. Oil components were added to the water components with continued stirring, without heat.
4. Finally glycols, protein hydrolysate and cellulose thickener were added.

This product provided a basic hair tonic ready for use.

For other products a more concentrated form was prepared which when added to a carrier formulation provided concentrations similar to those provided above. This concentrated hair complex comprised:

20 Concentrated Hair Stimulant Complex

<u>Component</u>	<u>Concentration</u> <u>(w/w%)</u>
Potassium acetate	0.5
Copper II acetate	0.25
25 Zinc acetate	0.25
Troxerutin	0.5

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	Theophyllisilane C	5.0
	Dimethyl silanol hyaluronate (available from Exsymol Ltd under the Trade Name "DSH C")	5.0
5	D-Panthenol	2.5
	Silicone Glycol Copolymer (available from Dow Corning under the Trade Name "Dow Corning 193")	7.5
10	Mixture of Zedoary, ginger and cinnamon oil (available from VEVY under the Trade Name "Zedomina")	2.5
	Vitamin A palmitate	0.25
	Vitamin E (available from Henkel under the Trade Name "Copherol F1300")	0.25
15	Onion extract and coconut oil (available from VEVY under the Trade Name "Allum Cepa")	0.5

The order and manner of mixing was as outlined above.

Example 2 Shampoo

- 20 Using the concentrated hair stimulant complex described above, a shampoo is prepared in conventional manner to the following composition:

	<u>Component</u>	<u>Concentration</u> <u>(w/v%)</u>
25	Xanthan Gum (available from Kelco International Ltd under the Trade Name "Keltrol")	0.4
30	Montmorillonite clay (available from English China Clays under the Trade Name "Gel White HNF")	2.0
	Ammonium lauryl sulphate (available from Albright & Wilson under the Trade Name "Empicol AL30T")	10.0

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	Sodium laureth sulphate (available from Albright & Wilson under the Trade Name "Empicol ESB 3/Y")	15.0
5	Sodium laureth sulphate (and) glycol distearate (and) cocamide MEA (available from Henkel under the Trade Name "Emperlan L53")	4.0
	Laureth-3 (available from Henkel under the Trade Name "Dehydol LS3")	1.0
10	Polyquaternium-7 (available from Calgon under the Trade Name "Merquat 550")	0.5
	Concentrated Hair Stimulant Complex (see above)	20.0
15	Mixture of glucose, glucose oxidase, lactoperoxidase, sodium iodide and sodium thiocyanate (available from the Boots Co PLC under the Trade Name "Myavert C")	0.9 0.05
	Bronopol	0.02
	Water	to 100

20 Example 3 "Leave-on" Conditioner

Using the concentrated hair stimulant complex described above, a "leave-on" conditioner is prepared in conventional manner to the following composition:

25	<u>Component</u>	<u>Concentration</u> <u>(w/w%)</u>
	Amodimethicone (and) tallow trimonium chloride (and) Nonoxynol 10 (available from Dow Corning under the Trade Name "Cationic Emulsion 929 DC")	1.5
30	Lauryldimonium hydroxypropyl hydrolysed collagen (available from Croda Chemicals under the Trade Name "Croquat L")	1.0
	Cetrimonium chloride (available from Henkel under the Trade Name "Dehyquart A")	2.0

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D-Panthenol 75L	0.2
Dipropylene glycol	0.24
Bronopol	0.02
5 Concentrated Hair Stimulant Complex (see above)	20.0
Water	to 100

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CLAIMS

1. The use of one or more of the following as hair stimulants:
 - 5 1) A water-soluble potassium, copper and/or zinc salt, suitably being an acetate salt;
 - 2) A flavone or flavone derivative, suitably comprising rutin, such as troxerutin;
 - 3) A xanthine, such as a theophylline, or a derivative thereof, such as methyl silanol theophyllin acetate
10 alginate;
 - 4) A mucopolysaccharide or derivative thereof such as dimethylsilanol hyaluronate;
 - 5) A fat soluble vitamin or a derivative thereof such as vitamin A (retinol) palmitate or vitamin E
15 (tocopherol);
 - 6) Zedoary, ginger, and/or cinnamon oil; or combinations of these;
 - 7) An allyl-based plant extract such as onion or garlic extract, such as onion extract in coconut
20 oil or garlic extracted in butylene glycol.
2. The use of any one, preferably two or three, of the substances listed in Claim 1 in the manufacture of a medicament for the treatment of hair loss, such as alopecia areata.
- 25 3. A method of treating hair loss (such as alopecia areata) by applying a flavone, a xanthine such as

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theophylline or a derivative thereof and at least one, suitably at least two of the other substances listed in Claim 1 to the scalp.

4. A composition for stimulating hair growth and/or
- 5 inhibiting hair loss in humans, comprising a flavone, a xanthine such as theophylline or a derivative thereof and at least one, suitably at least two of the other substances listed in Claim 1, for simultaneous or sequential administration to the scalp.

INTERNATIONAL SEARCH REPORT

Int. appl. No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/06 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 250 300 (SARL BFB ETUDES ET RECHERCHES EXPERIMENTALES) 23 December 1987 see	1,2
X	STN, File Supplier, Karlsruhe, DE, File Chemical Abstracts, vol 114, nA 157172 see the abstract	1,2
X	DE,A,37 24 259 (BRÜNNEN) 2 February 1989 see the whole document	1,2
X	DE,A,42 25 985 (KAO CORPORATION) 10 February 1994 see the whole document	1,2
X	GB,A,807 787 (WELLS) 21 January 1959 see the whole document	1,2

-/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* documents defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to undermine the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

12 February 1996

Date of mailing of the international search report

29.04.96

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Law and Application No.

PCT/EP 95/03861

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of documents, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 106 386 (BROOKE) 13 April 1983 see the whole document ---	1,2
X	DE,A,29 01 452 (SCHWECKENDIEK) 31 October 1979 see example 5 ---	1,2
X	FR,A,1 476 532 (FOURNIER) 14 April 1967 see ---	1,2
X	FR,A,2 282 856 (LOUIS) 26 March 1976 see the whole document ---	1,2
X	FR,A,2 587 208 (SCHERNINSKI) 20 March 1987 see the whole document ---	1,2
X	WO,A,94 15574 (BOURAS) 21 July 1994 see the whole document ---	1,2
X,P	PATENT ABSTRACTS OF JAPAN vol. 95, no. 001 (C) & JP,A.07 010 720 (TOMIHIKO YAMADA) see abstract ---	1,2
X	EP,A,0 334 486 (BEECHAM) 27 September 1989 see ---	1,2
X	WO,A,82 02833 (BAZZANO) 2 September 1982 see the whole document ---	1,2
X	FR,A,2 310 767 (DSA "PHARMACHIM") 10 December 1976 see the whole document -----	1,2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

International application No.

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Six different inventions were stated. For further information, please see enclosed form.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

International Application No. PCT/EP95/ 03861

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The problem underlying the present application is to provide a composition for use as hair stimulant, to provide a method of modifying hair growth and/or hair loss, and to provide uses of substances and/or compositions as hair stimulants.

The proposed solution consists of the use of certain compounds specified in claim 1.

EP-A-0250300 discloses soluble zinc salts in relation to the treatment of alopecia (see column 1, lines 27-36).

EP-A-0304466 discloses an ester of retinol in relation to hair care. FR-A-2310767 discloses vitamin A palmitate in relation to treatment of alopecia. WO-A-8202833 discloses retinoids in relation to increasing the rate of hair growth (see claims). These three documents were retrieved by random sampling from potentially relevant documents.

The idea to use the compounds mentioned in the claims as a solution to the above problem consequently is not novel, and cannot serve as a single general inventive concept, linking the uses of the compounds structurally specified in the claims.

The solutions presented in the present application therefore represent mere alternatives, not linked by a common inventive concept.

Rule 13.1-2 PCT requires that claimed alternatives are of a similar nature in having a common property or activity, and either a significant structural element shared by all of the alternatives, or in case a common structure is absent, all alternatives belonging to a recognised class of chemical compounds in the art to which the invention pertains (compare "Administrative Instructions under the PCT", Annex B, Unity of invention, paragraph (f)).

The claimed alternatives of groups 1) to 7) specified in claim 1 are of a similar nature in having a common property or activity, i.e. the hair stimulating activity. However, the groups 1) to 7) each do not share a significant structural element and each group of 1) to 7) represents a distinct recognised class of chemical compounds in the cosmetic and pharmaceutical art to which the invention pertains.

As a consequence the application relates to different inventions in which the used compounds are the groups 1) to 7) specified in claim 1.

The groups 1), 2), 3), 4), 5), 6), and 7) represent each (a series of) distinct inventions representing distinct recognised classes of chemical compounds in the cosmetic and pharmaceutical art to which the invention pertains.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed in the communication pursuant to Article 17(3)(a) PCT. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Searching these different subjects would have caused major additional searching efforts.

Only the first subject was searched.

YES 1. Claims 1-2 partially: The use of the compounds specified under 1) in claim 1.

NO 2. Claims 1-4 partially: The use/method/composition involving the compounds specified under 2) in claim 1, as far as not comprised in subject 1.

NO 3. Claims 1-4 partially: The use/method/composition involving the compounds specified under 3) in claim 1, as far as not comprised in subjects 1-2.

NO 4. Claims 1-2 partially: The use involving the compounds specified under 4) in claim 1, as far as not comprised in subjects 1-3.

NO 5. Claims 1-2 partially: The use involving the compounds specified under 5) in claim 1, as far as not comprised in subjects 1-4.

NO 6. Claims 1-2 partially: The use involving the compounds specified under 6) in claim 1, as far as not comprised in subjects 1-5.

NO 7. Claims 1-2 partially: The use involving the compounds specified under 7) in claim 1, as far as not comprised in subjects 1-6.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0250300	23-12-87	FR-A- 2599967 DE-A- 3772464	18-12-87 02-10-91
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GB-A-2106386	13-04-83	NONE	
DE-A-2901452	31-10-79	NONE	
FR-A-1476532	26-06-67	NONE	
FR-A-2282856	26-03-76	NONE	
FR-A-2587208	20-03-87	NONE	
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